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## Effectiveness of in-hospital geriatric co-management: a systematic review and meta-analysis

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### Abstract

**Background:** geriatric consultation teams have failed to impact clinical outcomes prompting geriatric co-management programmes to emerge as a promising strategy to manage frail patients on non-geriatric wards.

**Objective:** to conduct a systematic review of the effectiveness of in-hospital geriatric co-management.

**Data sources:** MEDLINE, EMBASE, CINAHL and CENTRAL were searched from inception to 6 May 2016. Reference lists, trial registers and PubMed Central Citations were additionally searched.

**Study selection:** randomised controlled trials and quasi-experimental studies of in-hospital patients included in a geriatric co-management study. Two investigators performed the selection process independently.

**Data extraction:** standardised data extraction and assessment of risk of bias were performed independently by two investigators.

**Results:** twelve studies and 3,590 patients were included from six randomised and six quasi-experimental studies. Geriatric co-management improved functional status and reduced the number of patients with complications in three of the four studies, but studies had a high risk of bias and outcomes were measured heterogeneously and could not be pooled. Co-management reduced the length of stay (pooled mean difference, –1.88 days [95% CI, –2.44 to –1.33]; 11 studies) and may reduce in-hospital mortality (pooled odds ratio, 0.72 [95% CI, 0.50–1.03]; 7 studies). Meta-analysis identified no effect on the number of patients discharged home (5 studies), post-discharge mortality (3 studies) and readmission rate (4 studies).

**Conclusions:** there was low-quality evidence of a reduced length of stay and a reduced number of patients with complications, and very low-quality evidence of better functional status as a result of geriatric co-management.

**Keywords:** *Co-management, review, geriatric, frail, outcome, older people, systematic review*

## Introduction

Older adults hospitalised on non-geriatric wards are at high risk of developing complications [1], disability [2] and unplanned readmissions [3]. The need for better in-hospital geriatric care has been voiced: [4] low quality of care has been observed in the management of dementia, delirium, depression and falls [5, 6].

Geriatric consultation teams have been implemented to recommend a plan of treatment for frail patients hospitalised on non-geriatric wards [7]. However, a meta-analysis observed only a beneficial effect on mortality at 6 and 8 months post-hospital discharge, without an effect on functional status, length of stay and readmission rate [8]. The non-adherence to recommendations and lack of control over patient care likely inhibit the effectiveness of these teams [9].

Geriatric co-management has been considered an alternative approach, and is defined as a shared responsibility and decision making between at least a treating physician (e.g. surgeon) and a geriatrician who provides complementary medical care in the prevention and management of geriatric-oriented problems [10]. Co-management interventions have previously been evaluated in systematic reviews focusing on ortho-geriatric care [11–15]. However, these reviews were restricted to the orthopaedic population, also included non-co-management interventions, were biased by a limited search strategy or inclusion of retrospective studies or did not explore clinical and methodological heterogeneity.

While there is an increasing interest in the implementation of co-management models [16], the limitations in the current systematic reviews and the exclusion of non-orthopaedic populations prevent informed decision-making. A new and more comprehensive systematic review is therefore warranted. We aimed to determine the effectiveness of in-hospital geriatric co-management on functional status, length of stay, mortality, readmission rate, complications and the number of patients discharged home up to 1-year follow-up. Secondly, we explored which study and intervention characteristics explain the observed effects.

## Methods

The review protocol was registered in PROSPERO (CRD42015026033) [17].

### Search strategy and data sources

A search string was co-developed with a library information specialist and piloted by one investigator. MEDLINE (Ovid SP), EMBASE (OVID interface), CINAHL (EBSCO health)

and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to 6 May 2016 (see Supplementary data, Supplement Table 2, available in *Age and Ageing* online). Systematic reviews were searched from inception to 6 May 2016 using the Cochrane Database of Systematic Reviews, PROSPERO, MEDLINE and EMBASE. Additional articles were searched in trial registers, reference lists from primary studies and systematic reviews, and through searching PubMed Central Citations.

### Study selection

Randomised controlled trials and quasi-experimental studies (non-randomised controlled trials with parallel groups, prospective before-and-after studies, interrupted time series) published in English, Dutch, German, French or Spanish were included if they sampled patients aged 65 years or older (or reported a mean age of 75 years or older). See Supplementary data, Supplement Text, available in *Age and Ageing* online for more details. Studies had to report the effect of an in-hospital geriatric co-management intervention on functional status, length of stay, mortality, readmission rate, complications or the number of patients discharged home up to 1-year follow-up. Interventions had to report co-management by a geriatrician or describe a shared responsibility or decision-making between a treating physician and a geriatrician for patients admitted on a non-geriatric ward. Co-management studies by other physicians (e.g. hospitalists) or health professionals (e.g. nurse practitioners) were excluded. Case reports, letters and abstracts were excluded. Two investigators piloted and performed the selection process independently. Discrepancies were resolved by consensus discussion and by two additional investigators.

### Data extraction and quality assessment

Data collection by one investigator was independently verified by a second investigator and included: (i) study characteristics, (ii) structure of co-management programmes, (iii) process of co-management programmes, (iv) intervention components and (v) outcome data (see Supplementary data, Supplement Text, available in *Age and Ageing* online). Discrepancies were resolved by consensus discussion.

The risk of bias was assessed independently by two of four investigators using the 'Methodological Index for Non-Randomised Studies' (see Supplementary data, Supplement Table 7 and Supplement Text, available in *Age and Ageing* online) [18]. Total scores range between 0 (high risk of bias) and 24 (low risk) based on consensus agreement.

## Data synthesis and analysis

Data were summarised using textual description and tabulation and were entered into RevMan (version 5.3) [19]. For continuous outcomes, the median and interquartile range (IQR), standard errors and confidence intervals were converted to mean and standard deviation [20, 21], and expressed as the mean difference (MD) with a 95% confidence interval (95% CI). Dichotomous outcomes were adjusted for mortality where appropriate, and expressed as an odds ratio (OR) with a 95% CI. Outcomes similarly defined by two or more studies on one endpoint at discharge, 30 days, 3 months, 6 months or 1 year follow-up were pooled in a meta-analysis. Continuous outcomes were pooled using the inverse variance method and binary outcomes using the Mantel-Haenszel method. All tests were performed using a fixed-effect model and using a random-effect model as sensitivity analysis. Statistical heterogeneity was explored using forest plots and  $I^2$  statistics for all pooled outcomes. Effect differences between studies were explored using study and intervention characteristics and risk of bias in subgroup analyses. A narrative synthesis was performed for outcomes that could not be pooled [22].

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to define the quality of the body of evidence as high,

moderate, low or very low (see Supplementary data, Supplement Text, available in *Age and Ageing* online) [20].

## Results

### Study selection

The search strategy identified 12,750 hits of which 335 were considered potentially relevant after screening title and abstract (see Figure 1. Flowchart). Twelve studies were included.

### Study characteristics

A total of 3,590 patients (1,626 receiving geriatric co-management) were included from six randomised controlled trials [23–28], one non-randomised controlled trial [29] and five prospective before-and-after studies [30–34]. All studies were single-centre and originated from Europe ( $n = 8$ ) [23, 25, 28, 30–34], North-America ( $n = 3$ ) [24, 27, 29] and Australia ( $n = 1$ ) [26]. Seven studies ended before 2000 [23–28, 30], four studies were conducted between 2000 and 2010 [29, 31–33] and one study ended in 2011 [34]. Seven studies included hip fracture patients [23, 26–28, 30, 33, 34], one study elective orthopaedic patients [32], three studies medical patients [25, 29, 31] and one study functional or mentally impaired patients [24]. The mean age of patients

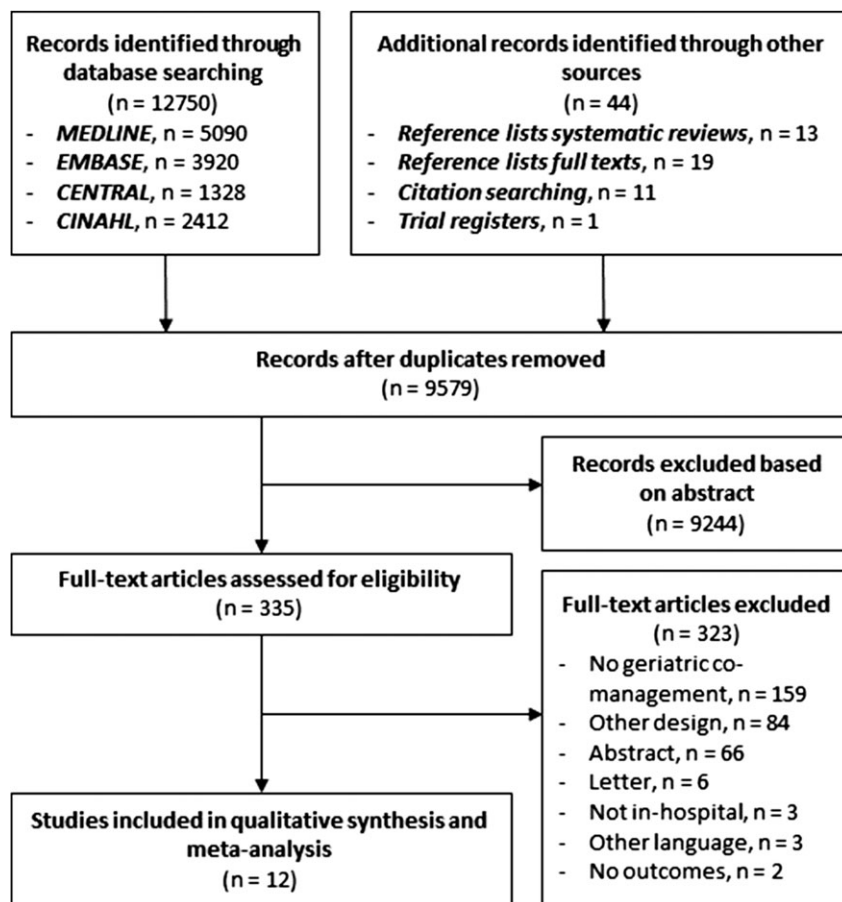


Figure 1. Flowchart.

Table 1. Study characteristics

Study	Country	Design	Study period	Population	Sample			
					Intervention group		Control group	
					<i>n</i>	Mean age (SD) <sup>a</sup>	<i>n</i>	Mean age (SD) <sup>a</sup>
Gilchrist 1988 [23]	UK	RCT	October 1984–July 1986	Women with hip fracture ≥65 years	97	82	125	80.6
Germain 1995 [24]	Canada, Quebec	RCT	July 1986–June 1987	Functional or mentally impaired elderly in-patients	56	81.9	52	80.1
Slaets 1997 [25]	Netherlands	RCT	October 1989–October 1990	Medical inpatients ≥75 years	140	83.2 (5.1)	97	82.5 (4.9)
Swanson 1998 [26]	Australia, Queensland	RCT	October 1994–July 1995	Hip fracture patients ≥55 years	38	78.5 (10.1)	33	77.8 (11.1)
Naglie 2002 [27]	Canada, Toronto	RCT	June 1993–March 1997	Hip fracture patients ≥70 years	141	83.8 (6.9)	138	84.6 (7.3)
Khan 2002 [30]	UK	Prospective before-and-after study	CG = January 1992–December 1994 IG = January 1995–December 1996	Elderly patients admitted for fractured femur neck	208	81	537	82
Vidan 2005 [28]	Spain	RCT	1 February–15 December 1997	Acute hip fracture surgery patients ≥65 years	155	81.1 (7.8)	164	82.6 (7.4)
Harari 2007 [32]	UK	Prospective before-and-after study	CG = May–July 2003 IG = August 2003–February 2004	Elective orthopaedic patients ≥65 years	54	74.1 (6.2)	54	75.0 (6.1)
Harari 2007 [31]	UK	Prospective before-and-after study	CG = August 2004 IG = August 2005	High-risk medical inpatients ≥70 years	49	83.0 (8.1)	46	80.7 (6.6)
Marsland 2010 [33]	UK	Prospective before-and-after study	CG = March–July 2004 IG = January–June 2006	Hip fracture patients	98	81.8	98	83
Arbaje 2010 [29]	USA, Maryland	nRCT	January–December 2007	Internal medicine patients ≥70 years	366	79.7 (5.7)	351	79.1 (5.6)
Suhm 2014 [34]	Switzerland	Prospective before-and-after study	CG = 1 June 2007–30 September 2008 IG = 1 April 2010–31 March 2011	Hip fracture patients ≥65 years	224	84.3 (7.4)	269	83.9 (7.5)

SD, standard deviation; RCT, randomised controlled trial; nRCT, non-randomised controlled trial; CG, control group; IG, intervention group.

<sup>a</sup>SD is reported when available or was obtained from the standard error [20].

ranged from 74 to 84 years (median = 82, IQR = 3). See Table 1 for study characteristics.

### Risk of bias

Risk of bias scores ranged between 11 and 23 (see Supplementary data, Supplement Table 7, available in *Age and Ageing* online). No multiple publications were identified. Selective reporting bias could not be evaluated in the absence of registered protocols. Publication bias could only be assessed for length of stay in a funnel plot that may indicate asymmetry (see Supplementary data, Supplement Figure 1, available in *Age and Ageing* online).

A summary of the meta-analyses is presented in Table 2.

### Effect on functional status

Functional status was assessed in four studies, but could not be pooled due to heterogeneity in outcome measurements (see Supplementary data, Supplement Table 3, available

in *Age and Ageing* online) [25–28]. At hospital discharge, co-managed patients had better functional status in two of three studies as they improved more in activities of daily living (ADL) [25] and level of dependency [25, 26], but not recovery of baseline ADL and mobility [28]. At 3-month follow-up, co-managed patients had better functional status in one of two studies as they recovered more in ADL or mobility [28], but not in level of dependency or ability to transfer [27]. At 6- and 12-month follow-up, co-managed patients did not differ in recovery of ADL [28], mobility [27, 28], transfers [27] and level of dependency [27]. The differences in the observed effects between studies likely result from a difference in risk of bias favoring co-management due to multiple testing [25], missing data [25, 28] and co-intervention [25].

### Effect on length of stay

Length of stay was assessed in 11 studies (see Supplementary data, Supplement Figure 2, available in *Age and Ageing* online) [23–32, 34], and was reduced in five intervention groups

Table 2. Pooled effects of geriatric co-management

Outcome	Number of studies	Number of patients	Fixed-effect model [95% CI]	$I^2$	Random-effect model [95% CI]	GRADE <sup>a</sup>
Length of stay	11	3,394	MD, -1.88 [-2.44 to -1.33]	86%	MD, -2.62 [-4.72 to -0.53]	Low
In-hospital mortality	7	1,492	OR, 0.72 [0.50 to 1.03]	19%	OR, 0.70 [0.44 to 1.10]	Low
Mortality at 30-day follow-up	3	796	OR, 0.94 [0.53 to 1.69]	0%	OR, 0.95 [0.53 to 1.70]	Very low
Mortality at 3-month follow-up	3	697	OR, 0.88 [0.58 to 1.33]	50%	OR, 0.88 [0.48 to 1.61]	Very low
Mortality at 6-month follow-up	3	572	OR, 0.65 [0.42 to 1.01]	0%	OR, 0.65 [0.42 to 1.01]	Very low
Mortality at 12-month follow-up	3	926	OR, 1.07 [0.79 to 1.44]	77%	OR, 0.91 [0.46 to 1.81]	Very low
Readmission rate at 30-day follow-up	3	695	OR, 1.28 [0.71 to 2.31]	24%	OR, 1.24 [0.60 to 2.57]	Very low
Readmission rate at 12-month follow-up	2	601	OR, 0.91 [0.64 to 1.29]	0%	OR, 0.91 [0.64 to 1.29]	Very low
Number of patients discharged home	5	1,370	OR, 1.07 [0.86 to 1.34]	67%	OR, 1.24 [0.78 to 1.98]	Very low

CI, confidence interval; MD, mean difference; OR, odds ratio.

<sup>a</sup>GRADE = Grading of Recommendations Assessment, Development and Evaluation and defines the quality of the body of evidence. Low GRADE evidence indicates that 'further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate' [44]. Very low GRADE evidence indicates that 'our group is uncertain about the estimate' (see Supplementary data, Supplement Table 5, available in *Age and Ageing* online) [44].

[24, 26, 28, 32, 34]. The length of stay was increased in one intervention group [27]. However, the authors anticipated this effect as the intervention included a more intensive in-hospital intervention as compared to standard of care. Co-management reduced overall length of stay (MD, -1.88 [95% CI, -2.44 to -1.33];  $I^2 = 86%$ ; 3,394 patients). This result was robust in a random-effect model (MD, -2.62 [95% CI, -4.72 to -0.53]), but the heterogeneity could not be explained. The reduced length of stay corresponds to a low standardised effect size (-0.17 [95% CI, -0.23 to -0.10] for the fixed-effect model and -0.27 [95% CI, -0.48 to -0.05] for the random-effect model). This effect disappeared in studies at low risk of bias (0.03 [95% CI, -0.34 to 0.40]; see Supplementary data, Supplement Table 6, available in *Age and Ageing* online).

### Effect on mortality

In-hospital mortality was assessed in seven studies (see Supplementary data, Supplement Figure 3, available in *Age and Ageing* online) [23, 24, 26–28, 30, 34], and was reduced in one intervention group [28]. Co-management reduced in-hospital mortality (OR, 0.72 [95% CI, 0.50–1.03];  $I^2 = 19%$ ; 2,237 patients), but this was not statistically significant. Subgroup analysis identified a reduced odds of in-hospital mortality when excluding one large prospective before-and-after study at high risk of bias that did not report co-management roles for non-medical professionals (e.g. physical therapist) [30] as compared to studies who did (OR, 0.50 [95% CI, 0.30–0.83];  $I^2 = 0%$ ; 1,492 patients; 6 studies) [23, 24, 26–28, 34].

Post-discharge mortality was assessed in three studies at 30 days [32–34], 3 months [23, 27, 33], 6 months [23, 26, 27] and 12 months follow-up (see Supplementary data, Supplement Figure 4, available in *Age and Ageing* online) [24, 28, 34]. Co-management had no effect on post-discharge mortality at 30 days (OR, 0.94 [95% CI, 0.53–1.69];  $I^2 = 0%$ ; 796 patients), 3 months (OR, 0.88 [95% CI, 0.58–1.33];  $I^2 = 50%$ ; 697 patients), 6 months (OR, 0.65 [95% CI, 0.42–1.01];  $I^2 = 0%$ ; 572 patients) and 12 months follow-up (OR, 1.07 [95% CI, 0.79–1.44];  $I^2 = 77%$ ; 926

patients). Subgroup analysis could explain the observed statistical heterogeneity by excluding two studies at high risk of bias favoring standard of care due to confounding bias [33, 34], but the effects remained non-significant.

### Effect on readmission rate

Readmission rate was assessed in six studies [24, 25, 28, 31, 32, 34], and was reduced at 6-month follow-up in one intervention group (OR, 0.49 [95% CI, 0.26–0.92]) [25]. Three studies were pooled at 30-day follow-up [31, 32, 34], and two studies at 12-month follow-up (see Supplementary data, Supplement Figure 5, available in *Age and Ageing* online) [24, 34]. Co-management had no overall effect on readmission rate at 30-day follow-up (OR, 1.28 [95% CI, 0.71–2.31];  $I^2 = 24%$ ; 695 patients) [31, 32, 34], nor at 12-month follow-up (OR, 0.91 [95% CI, 0.64–1.29];  $I^2 = 0%$ ; 601 patients) [24, 34].

### Effect on complications

In-hospital complications were assessed in four studies, but could not be pooled due to heterogeneity in outcome measurements (see Supplementary data, Supplement Table 4, available in *Age and Ageing* online) [28, 32–34]. Co-managed patients had a lower number of complications (OR, 0.10 [95% CI, 0.05–0.20]) [32]. Likewise, co-management resulted in a lower number of patients with one or more complications (OR, 0.52 [95% CI, 0.36–0.77]) [34], and in a lower number of patients with major complications (OR, 0.46 [95% CI, 0.29–0.72]) [28]. One study did not report sufficient data to extrapolate an effect [33]. These results suggest a risk reduction between -14% and -54% which equals a number needed to treat (NNT) between 7 and 2 patients. The differences in the observed effects between studies likely result from a difference between studies in risk of bias favouring co-management.

### Effect on patients discharged home

The number of patients discharged home was assessed in five studies [23, 24, 27, 29, 33]. More patients were discharged home as a result of geriatric co-management in two

individual studies (see Supplementary data, Supplement Figure 6, available in *Age and Ageing* online) [24, 27]. Co-management had no overall effect on the number of patients discharged home (OR, 1.07 [95% CI, 0.86–1.34];  $I^2 = 67\%$ ; 1,370 patients; 5 studies). Subgroup analysis identified more patients being discharged home when discharge planning was an intervention component (OR, 3.00 [95% CI, 1.48–6.06];  $I^2 = 0$ ; 235 patients; 2 studies) [24, 27]. As a result, 16.2% more patients were discharged home which equals a NNT of 6 patients.

## Discussion

This systematic review determined the effect of in-hospital geriatric co-management and included 12 studies and 3,590 patients. We observed very low-quality evidence for better functional status and low-quality evidence for reducing length of stay and preventing complications as a result of geriatric co-management (see Table 2 and Supplementary data, Supplement Table 5, available in *Age and Ageing* online). The effect on length of stay ranged between  $-7.2$  and  $3.4$  days but subgroup analyses could not explain this dispersion. However, based on the direction of the effect, we infer that co-management will likely reduce length of stay. The effect size was small for functional status and moderate for preventing complications. In-hospital mortality was reduced but this was not statistically significant. No effects were observed for post-discharge mortality, readmission rate and number of patients discharged home.

We explored which study and intervention characteristics explained the effects. This mostly related to risk of bias overestimating treatment effects on functional status, complications and length of stay. The effect on length of stay disappeared when only studies at low risk of bias were included. In-hospital mortality was reduced in RCT's but this may also reflect sampling error by the subgroup analysis (see Supplementary data, Supplement Table 6, available in *Age and Ageing* online). In-hospital mortality was reduced when co-managing patients in a multi-professional team (also including non-physicians). More patients were discharged home when discharge planning was defined as an explicit intervention component.

Subgroup analyses detected no substantial differences in effect between orthopaedic and medical patients (see Supplementary data, Supplement Table 6, available in *Age and Ageing* online). However, the effect in medical patients could only be assessed for the outcomes length of stay, patients discharged home and 30 days readmission rate. Nonetheless, geriatric syndromes are prevalent in older medical patients [35] and these patients experience poor functional outcomes [36]. Care based on the principle of comprehensive geriatric assessment (CGA) could therefore be promising for these patients.

CGA is characterised by a 'multidimensional, interdisciplinary diagnostic process to determine the medical, psychological and functional capabilities of an older person with frailty, followed by the implementation of a coordinated and integrated plan for treatment and follow-up' [7].

Previous meta-analyses have indicated that CGA on geriatric wards resulted in less functional decline at discharge and more patients being alive and living at home after hospitalisation, but not when implemented by a geriatric consultation team [8, 37, 38]. Our review indicates that co-management may be superior to consultation as a model for CGA on non-geriatric wards. Three systematic reviews have previously evaluated the effectiveness of geriatric co-management in orthopaedic patients. Two meta-analyses were performed: [13, 14] length of stay was reduced in one analysis [13], but no effects were observed on mortality, functional status and time to surgery. Both meta-analysis included different studies (compared against each other and against this review) and had low statistical power. One narrative analysis concluded that co-management was associated with the lowest in-hospital mortality rate, length of stay and time to surgery [11], but it was unclear how the authors reached this conclusion.

There are important differences between reviews in the inclusion and classification of co-management studies [11–15]. This likely reflects a difference in search strategy and clinical differences between co-management programmes and their definitions. The supplement of our manuscript details the intervention characteristics. While most studies included a physical therapist, performed rehabilitation and organised ward rounds, only half included social workers and performed discharge planning, and less than half included a geriatric nurse, participated in multidisciplinary meetings or used evidence-based protocols. These differences highlight an important consideration: the effect of co-management will depend largely on how programmes are organised and implemented and how the programme interacts with its context [39]. For example, in-patient geriatric rehabilitation improves functional status [40], outpatient geriatric follow-up may improve survival [41] and our results suggest that including interdisciplinary teams- and proactive discharge planning in co-management interventions may improve in-hospital survival and discharge disposition.

However, further research is needed. First, co-management effects in hip fracture patients have been replicated sufficiently to warrant cluster RCT's and increase the quality of the evidence. Prospective quasi-experimental studies with sufficient case-mix variables to adjust for baseline confounding may be considered to further explore the effects in non-orthopaedic populations. Secondly, analyses should focus on (post-discharge) functioning and cognition, and should determine the cost-effectiveness. Thirdly, a better understanding is needed on what constitutes an effective geriatric co-management programme. Several sources of variation in effects should be considered: the differences in patient case-mix, structure and processes of co-management and the implementation of programmes. Process evaluations can be used to identify contextual factors, intervention theory and core mechanisms of impact to facilitate implementation [42].

## Methodological considerations

This review included non-randomised controlled studies as individual randomisation can result in contamination bias.

Confounding and selection may therefore have biased the co-management effect, but this proved hard to assess due to poor reporting of study methodology. A fixed-effect model was used, despite heterogeneity, due to the low number of included studies, the risk of bias in smaller studies and the high likelihood of publication bias [43]. While a random-effect model did not change the conclusion, we caution readers about inferring an exact treatment effect. The assessments of mortality, hospital readmission and number of patients discharged home suffered low statistical power and a clinically significant reduction remains possible within the limits of the confidence intervals. Subgroup analyses were used to explain differences in effect estimates between studies, but these results may be biased by both multiple testing and low statistical power, and should be considered hypothesis generating evidence.

## Conclusions

There was low-quality evidence of a reduced length of stay and a reduced number of patients with complications, and very low-quality evidence of better functional status as a result of geriatric co-management. These results suggest that geriatric co-management has a potential benefit for managing frail patients admitted to a non-geriatric ward, but there is a high degree of uncertainty related to both the association and magnitude of the effect. Further research should therefore be considered a priority before considering scaling-up geriatric co-management programmes throughout health systems.

## Key points

- Geriatric co-management has a low to moderate effect on complications, functional status and length of stay.
- For hip fracture patients, a cluster RCT is needed to replicate the effects and improve the quality of evidence.
- Future studies should focus on non-orthopaedic populations, patient-centred outcomes, cost-effectiveness and process evaluation.
- The current quality of evidence does not support a large scale implementation of geriatric co-management programmes.

## Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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## Author's contributions

Conception or design: all authors; Acquisition, analysis or interpretation of data: B.V.G., J.F., A.L., K.M., M.D.; Drafting the manuscript: B.V.G.; Critical revision of the manuscript for important intellectual content: all authors; Statistical analysis: B.V.G., A.L.; Obtaining funding: J.F., K.M., M.D.; Supervision: M.D.

## Conflicts of interest

Dr Rex reports personal fees from Orion Pharma, B Braun, AirLiquide Medical and Edwards Lifesciences, outside the submitted work. The other authors report no conflict of interest.

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(The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website as supplement references.)

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